REMARKS

The Official Action of December 29, 2005, and the prior art relied upon therein have been carefully reviewed. The claims in the application are now claims 1-14 and 16-20, and these claims define patentable subject matter warranting their allowance. Applicant accordingly respectfully requests favorable reconsideration and allowance.

Acknowledgement by the PTO of the receipt of applicant's papers filed under Section 119 is noted.

Applicant does not understand any deficiency which might exist in the present application with respect to paragraph 2 on page 2 of the Office Action under the heading "priority", as the first paragraph of applicant's specification and the Application Data Sheet are both believed to be fully complete with respect to both priority and benefit.

Applicant also does not understand paragraph 4 of on page 2 of the Official Action under the heading "Information Disclosure Statement", as applicant is unaware of what documents the Examiner is referring to which appear in the specification but not in any proper IDS. Clarification is respectfully requested.

With respect to paragraph 8 on page 2 of the Office Action under the heading "Specification", applicant is unaware of any possible minor errors.

However, the Examiner is thanked for pointing out the clerical error on page 5, line 24, which has now been corrected above.

As regards page 1 of the specification not being numbered, applicant notes that it is common (indeed usual) for the first page to be unnumbered. Nevertheless, the Examiner is hereby authorized to insert the page number on the first page of applicant's specification, if the Examiner remains adamant.

Claim 2 and its dependent claims 3-7 and 17-20 have been rejected under the second paragraph of Section 112. The rejection is respectfully traversed.

First, there is nothing wrong with the word "early" with respect to the expression "early atherosclerosis", as this is common and accepted terminology, e.g. note paragraphs [0002], last line, and paragraph [0003] at page 2 lines 5 and 6, and line 7, as well as in paragraph [0004], line 4 thereof. Attention is particularly invited to paragraph [0010] commencing near the bottom of page 4.

Thus, applicant respectfully disagrees that this term is indefinite. In the parent application, applicant pointed out that the term "early atherosclerosis" is not only described in the application, but applicant submitted a publication in the

name of Skalen et al appearing in Nature, showing that the term "early atherosclerosis" is a conventionally used term within the field.

Nevertheless, claim 2 has been amended to delete reference to the word "early", claim 2 now referring to diagnosing a risk of atherosclerosis, support being found for example in the first sentence of paragraph [0002], which refers to embodiments of the present invention providing methods for identifying patients who have an increased **risk** of atherosclerosis.

The Examiner further queries how a diagnosis of cardiovascular disease will also determine independent disorders like atherosclerosis, hypertension and thrombosis.

According to the literature, cardiovascular disease (CVD) refers to all diseases and conditions involving the heart and blood vessels, including stroke, which is a common cause of **thrombosis**. The underlying cause of most CVD is a gradual clogging of the arteries (**atherosclerosis**) that supply blood to the heart, brain, and other vital organs. Cardiovascular disease further include arteriosclerosis, coronary artery disease, heart valve disease, arrhythmia, heart failure, **hypertension**, orthostatic hypertension, shock, endocarditus, disease of the aorta and its branches, disorders of the peripheral vascular system, and congenital heart disease.

Therefore, while applicant's claimed subject matter does not distinguish early atherosclerosis, hypertension and thrombosis from other cardiovascular disease, **they are included in the term,** i.e. a patient suffering from one of these conditions can use the claimed method and the condition will be uncovered. Moreover, please note that a similar formulation was approved in the parent application (claim 2 thereof).

Thus, atherosclerosis, hypertension and thrombosis are all *types of* cardiovascular disease. Claim 1 encompasses diagnosis of cardiovascular diseases, and the risk thereof, generally; whereas Claim 2 specifies particular types of cardiovascular diseases that can be diagnosed. There is no question of Claim 2 implying that the claimed method can detect *different diseases in addition to* cardiovascular disease (as suggested by the examiner); on the contrary, Claim 2 provides a clear teaching to the reader in respect of particular types of cardiovascular disease that can be diagnosed by the claimed methods. Accordingly, the claims are clear without further amendment.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1-20 have been provisionally rejected on the basis of obviousness-type double patenting over claims 1-13 of applicant's U.S. patent 6,780,605 which issued from parent application 09/720,967. The rejection is respectfully traversed.

Applicant notes from the Examiner's comment at the middle of page 2 in italics that the Examiner was unable to ascertain if claims corresponding to the present invention were restricted from parent application 09/720,967, and invites applicant to show evidence of such a restriction requirement. There was a restriction requirement in the parent application, but the file of undersigned is in storage and not available to meet the present due date. However, copies of the Replies of July 26, 2002, and January 29, 2003, have been copied from computer memory and are attached hereto as attachments A and B.

Applicant briefly and respectfully notes that the presently claimed embodiments go well beyond the claims of the of the parent application in the sense of being non-obvious therefrom, as will be apparent from the remarks below (commencing at the bottom of page 14) in reply to the first prior art rejection.

As the rejection is provisional, applicant need not further reply at the present time.

Claims 1-13 have been rejected as obvious under section 103 from Barquinero et al, reference AC (Barquinero) in view of Ostermann et al, reference AJ (Ostermann). This rejection is respectfully traversed.

As understood, the rejection appears to be based on the conclusion that it would have been obvious to measure PAF concentrations in the serum and plasma of patients with

cardiovascular disease and to discriminate between low and high risk groups. However, this conclusion suggests a misunderstanding of the nature of the currently pending claims. The method held to be obvious in view of the combination of Barquinero and Ostermann is *a totally different method* from the claimed method.

Thus, claim 1 relates to a method of diagnosing cardiovascular disease by testing a sample of body fluid from a patient for the presence and/or concentration of antibodies that can bind to phosphocholine and/or a derivative thereof. Such derivatives can be e.g. phosphorylcholine and lysophosphatidylcholine.

The rejection correctly accepts on page 6 of the outstanding Office Action that Barquinero does not disclose platelet activating factor (PAF) as an indicator of cardiovascular disease.

Moreover, as discussed in the prosecution of US Patent No. 6,780,605 (US parent Patent Application No. 09/720,967), in the response dated 25 June 2003, Barquinero mentions that serum from a patient with thrombotic manifestations showed high specific binding to PAF, but this does not imply that antibodies against PAF (aPAF) may be used to diagnose or predict vascular disease since the patient already had thrombotic manifestations when this specific binding was demonstrated. Furthermore, Barquinero mentions aCL (i.e. antibodies to cardiolipin), in

addition to aPAF, and there is nothing indicating that only aPAF should be used.

Thus, in view of the above, one can draw the following conclusions about the teaching of Barquinero-

- It does not teach that PAF is an indicator of the risk of cardiovascular disease; and
- It does not teach that antibodies to PAF (i.e. aPAF) are an indicator of the risk of cardiovascular disease.

The person of ordinary skill in the art cannot find or extrapolate from the disclosure of Barquinero that PAF is an indicator of the risk of cardiovascular disease, or that antibodies to PAF (i.e. aPAF) are an indicator of the risk of cardiovascular disease.

Accordingly, Barquinero does not to make obvious a method of diagnosing cardiovascular disease by assessing the binding of antibodies to PAF. The present examiner has acknowledged this by the granting of US Patent No. 6,780,605, which claims such a method.

Furthermore, the examiner has also acknowledged that the same claims are non-obvious from the combination of Barquinero and Ostermann. As explained in the Reply dated 25 June 2003 in the parent application, Ostermann had not been cited to make up for the deficiencies of Barquinero and, indeed, does not do so. Ostermann teaches the measuring of PAF levels in

serum and plasma from patients suffering from coronary artery disease and further teaches that PAF could be used to discriminate between low and high-risk groups of patients. However, Ostermann does not measure *antibodies to* PAF (i.e. aPAF), but rather PAF itself.

There are no data or information whatsoever in Ostermann, suggesting or even remotely inferring to a person skilled in the art that aPAF and PAF are closely related at all, much less that their presence in the body of a patient would have the same clinical significance when it comes to diagnosing risk of cardiovascular disease. Accordingly, Ostermann completely fails to provide even the slightest hint to the person of ordinary skill in the art that a measurement of the levels of aPAF can be useful in determining the risk of cardiovascular disease.

It was on this basis that the present examiner withdrew the previous rejections based on Barquinero and Ostermann, and granted US Patent No. 6,780,605.

The method encompassed by the claims of the present application is *even further removed* from the teachings of Barquinero and Ostermann. As discussed above, Claim 1 relates to a method of diagnosing cardiovascular disease by testing a sample of body fluid from a patient for the presence and/or concentration of antibodies that can bind to phosphocholine and/or a derivative thereof.

As discussed above, neither Barquinero, nor Ostermann, make it obvious to assay the concentrations and/or levels of *antibodies to* PAF in a patient's sample in order to determine risk of cardiovascular disease. It is even less obvious that one can also use ligands other than PAF, in the present case phosphocholine and/or a derivative thereof, to determine risk of cardiovascular disease.

The person skilled in the art, following the teaching of Ostermann would test for levels of PAF, and would not consider testing the levels of *any* antibodies, much less the levels of antibodies to phosphocholine and/or a derivative thereof as claimed in the present application.

Even if the reader of Ostermann were to consult Barquinero (for which there is really no motivation), it is to be noted that -

(i) the reader of Ostermann, when wishing to assess the risk of cardiovascular disease, would not have been motivated by Barquinero to measure aPAF levels instead of measuring PAF levels because (as discussed above) Barquinero does not teach that antibodies to PAF (i.e. aPAF) are an indicator of the risk of cardiovascular disease at all; and

(ii) even if (i) were not the case, Barquinero additionally does not teach the person skilled in the art that phosphocholine and/or a derivative thereof can be useful

in binding antibodies that are clinically significant in determining the risk of cardiovascular disease.

Thus, the claims of the present application are non-obvious from Barquinero and Ostermann, either individually or in combination.

As the present invention would not have been obvious from a consideration together of Barquinero and Ostermann, the rejection should be withdrawn. Such is respectfully requested.

Claims 14-20 have been rejected as obvious from Barquinero in view of Ostermann and further in view of Karasawa et al, reference AH (Karasawa). This rejection is respectfully traversed.

Applicant believes and respectfully submits that the PTO has not correctly assessed claims 14-20. In this regard, the rejection states as follows:

> *Barquinero et al. in view of and Ostermann et al. differ from the instant invention in not specifically teaching the detection of various known naturally occurring phospholipids related to PAF(phospholine). These forms include lysoPAF, PC(phosphatidylcholine), and lysoPC(lysophosphatidylcholine).*

This statement contains two key inaccuracies -

- The instant invention *does not relate to the detection of naturally occurring phospholipids*; on the contrary it relates to the detection of antibodies to the phosphocholine and/or derivatives thereof. Claims 14-20 specify the

identity of the ligand used to capture antibodies from a body fluid sample, not the identity of the chemical entity that is captured by the claimed method. In other words, methods of detection of naturally occurring phospholipids and methods of detection of antibodies to the phosphocholine and/or derivatives thereof are clearly not at all the same. If the examiner wishes to extend the teachings of Barquinero and Ostermann to the present claims, it would be necessary to explain why -

(a) the person skilled in the art should expect that phosphocholine and/or derivatives thereof should be expected to have the same clinical relevance to the assessment of risk of cardiovascular disease as the reported link between PAF levels and cardiovascular disease as reported in Ostermann; and

(b) even if phosphocholine and/or derivatives thereof should be expected to have the same clinical relevance to the assessment of risk of cardiovascular disease, why the levels of antibodies to those molecules should be assessed in determining the risk of cardiovascular disease.

There is nothing in any of the cited prior art documents that teaches or even remotely suggests that either of (a) or

(b) would have been expected by the person of ordinary skill in the art.

- The rejection refers to "*PAF(phospholine)*". PAF is an acronym for platelet activating factor, not "phospholine". Applicant is unsure why the rejection referred to "phospholine" here, but firstly it is wrong to consider PAF to be phospholine; and secondly one should not confuse phospholine with "phosphocholine" as mentioned in the present claims.

The PTO refers to Karasawa as motivation to use various phospholipids to evaluate cross-reactivity and allow for the accurate detection of PAF antibodies in the kit of Barquinero, thereby to draw the conclusion that it is obvious to assess risk of cardiovascular disease by determining the levels of antibodies to phosphocholine and/or derivatives thereof in a sample of body fluid.

With respect, such allegation is flawed - as discussed above, it is not obvious from Barquinero, or Ostermann, alone or in combination, that one could assess the risk of cardiovascular disease by determining the levels of antibodies to phosphocholine and/or derivatives thereof in a sample of body fluid. Karasawa has not been cited to make up for these deficiencies in Barquinero and Ostermann. Nor, indeed, does it do so.

Furthermore, contrary to the rejection, Karasawa discloses a system for the detection of PAF, *not for the*

detection of aPAF. Specifically, Karasawa discloses the development of the radioimmunoassay method to measure levels of PAF (not *antibodies to* PAF) in a biological sample.

The test of Karasawa uses serum obtained from a PAF-immunised rabbit. This serum contains a mixture of different antibodies that contains, amongst others, antibodies to PAF. Karasawa teaches that the serum is used to detect PAF in a sample. Page 1127, second column, first paragraph of the "results" section, reports that "*For the radioimmunoassay, we used antiserum collected after the fourth injection*".

The radioimmunoassay of Karasawa involves measuring the level of PAF in a sample by measuring the ability of any PAF in that sample to compete with radio-labelled PAF to bind to antibodies in the rabbit antiserum. This method does not measure the levels of *any antibodies*, much less the levels of antibody to phosphocholine and/or derivatives thereof, in the collected antiserum. On the contrary, the antiserum that is collected was used by Karasawa *et al* as a tool in the quantification of PAF in a sample of choice.

Since the collected antiserum used in the radioimmunoassay of Karasawa contained a *mixture* of antibodies from the rabbit, some (in fact most) of the antibodies in the sample clearly would not be specific to PAF. Accordingly, competitive inhibition of binding of the radio-labelled PAF to the antiserum, by compounds in the biological sample being

tested, could potentially be due to the presence of an antibody in the antiserum that has a non-specific binding affinity both for PAF and also other molecules in the biological sample tested, and those other molecules being able to compete with, and inhibit the binding of, radio-labelled PAF to this non-specific antibody in the antiserum. In that case, the radioimmunoassay could not be used to reliably quantify the level of PAF in a sample.

Because of this potential problem, Karasawa *et al* wanted to check that they were observing a specific binding of PAF in the competitive radioimmunoassay. To do this, they compared the binding of the antiserum to other PAF-like molecules. Page 1128, second column, lines 2-8 reports that:

> *Cross-reactivity studies of the antiserum revealed a high specificity for PAF. Choline-containing phospholipids such as lysoPAF, lecithin or lysoPC did not cross-react with PAF antiserum (Table 1)* (emphasis added).

In other words, Karasawa *et al* satisfied themselves that the antiserum sample that they obtained could be reliably used to measure the level of PAF in a sample, because the antiserum did not contain any antibodies that would non-specifically bind both PAF and other PAF-like molecules.

Likewise, in Barquinero, page 57, left hand column, the authors reported that anti-PAF antibodies that had been affinity purified using PAF as a ligand did not cross react with

phosphatidylcholine and other phospholipids (see section entitled "*Affinity purified anti-PAF*"). The section that follows (entitled "*Inhibition studies*") reports that the binding of PAF to affinity-purified IgM anti-PAF antibodies could be inhibited by the presence of phosphatidylcholine, which suggests that some anti-PAF antibodies can also bind to phosphatidylcholine, but that section also reports that "*PAF produced the highest inhibition*" which tells the reader that the best way to capture such antibodies is to use PAF as an affinity ligand.

Therefore, the teaching of both Karasawa and Barquinero is that, generally, anti-PAF antibodies do not bind to other PAF-like molecules and, where they do (such as in the case of the binding of IgM anti-PAF antibodies to phosphatidylcholine, as discussed in Barquinero) then such antibodies still bind more strongly to PAF itself.

Accordingly, in light of the teaching of Barquinero, either alone or in combination with the teaching of Karasawa, the skilled person would be motivated to use PAF alone to determine the presence of anti-PAF antibodies in a sample.

There is no motivation in either of Barquinero or Karasawa to test a sample of body fluid for the presence of antibodies other than anti-PAF antibodies (because there is no indication that such antibodies exist, much less that they have any clinical significance). Accordingly, in light of the teaching of Barquinero, alone or in combination with Karasawa,

the skilled person would only be motivated to determine the presence of anti-PAF antibodies in a sample from a patient and, as discussed above, the teaching of Barquinero is then that, to the extent that one wishes to determine the presence of anti-PAF antibodies, one should use PAF as a ligand to capture such antibodies.

Therefore, it would not have been obvious, in light of the three prior art documents, to use any of phosphocholine, phosphorylcholine or lysophosphatidylcholine to determine the levels, in a patient's sample, of antibodies that bind to these compounds, much less to do so for the purposes of determining the risk of cardiovascular disease.

Furthermore, phosphocholine, phosphorylcholine and lysophosphatidylcholine are smaller, more simple molecules than PAF, and accordingly comprise fewer epitopes than PAF. As a result, the use of phosphocholine, phosphorylcholine and/or lysophosphatidylcholine as a ligand provides the user with the ability to bind a more specific group of antibodies. This added advantage was not appreciated in the cited art.

In summary, the cited prior art teaches the person of ordinary skill in the art to continue to use PAF to assess the risk of cardiovascular disease (Ostermann). None of Ostermann, Barquinero, or Karasawa teach, or even remotely suggest, that antibodies to PAF could be relevant to the determination of the risk of cardiovascular disease. Even if there were, there is

certainly no indication in any of the these documents that phosphocholine and/or derivatives thereof should be used as a ligand to capture antibodies from a body fluid sample, thereby to assess the risk of cardiovascular disease.

Accordingly, none of applicant's claims would have been obvious to a person of ordinary skill in the art at the time the present invention was made from a consideration together of Barquinero, Ostermann and Karasawa. The rejection should be withdrawn and such is respectfully requested.

Applicant believes that all issues raised in the Office Action have been addressed above in a manner favorable to allowance of the present application. Accordingly, applicant respectfully requests favorable reconsideration and early formal allowance.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: FROSTEGARD=1A

In re Application of:	)	Art Unit: 1641
Johan FROSTEGARD	)	Examiner: L. V. Cook
Appln. No.: 09/720,967	)	Washington, D.C.
Date Filed: April 6, 2001	)	Confirmation No. 8281
For: METHOD OF DIAGNOSING CARDIOVASCULAR DISEASE...	)	July 26, 2002 ~~March 29, 2006~~

REPLY TO RESTRICTION REQUIREMENT

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

Replying to Paper No. 8, the Office Action mailed July 3, 2002, please amend as follows:

IN THE CLAIMS

Please amend the claim by rewriting claim 13 in amended form as follows (attached hereto is a marked-up version of the changes made to the claim captioned "Version with Markings to Show Changes Made"):

13. (Amended) The method of claim 11, wherein said diagnosis of a cardiovascular disease comprises a diagnosis of early atherosclerosis, hypertension or thrombosis.

REMARKS

The Official Action mailed July 3, 2002, substantially only in the nature of a restriction requirement, has been carefully reviewed. The claims in the application

Attachment A

remain as claims 11-31, and the dependency of claim 13 has now been corrected; the examiner is thanked for pointing out the clerical error in claim 13. Applicant requests favorable consideration.

The present application is the U.S. national phase of a PCT application claiming priority from a Swedish application filed July 3, 1998, and from a U.S. provisional application filed July 6, 1998. The Form PCT/DO/EO/903 indicates that the "Priority Document" has been received, (along with copies of the International Search Report and references cited therein). Applicant respectfully requests the examiner to acknowledge receipt of applicant's papers filed under Section 119.

Restriction has been required between what the examiner considers to be two patentably distinct inventions as outlined on page 2 of the Office Action. As applicant must make an election even though the requirement is traversed, applicant hereby provisionally and respectfully elects Group I, presently said by the PTO to comprise claims 11, 12, 14-19 and 25-31, with traverse and without prejudice.

The PTO recognizes that normal restriction practice does not apply because the present application is the U.S. national phase of a PCT application, wherein by international treaty the PTO is obligated to follow the PCT rules involving unity-of-invention rather than normal U.S. restriction practice. The PTO states that there is lack of unity-of-invention because the two groups do not share the same or corresponding special technical feature or features. Applicant respectfully disagrees. The same or corresponding special technical feature is the subject matter of claim 11,

it being noted that all the claims depend from and incorporate the subject matter of claim 11.

Applicant also respectfully notes that no lack of unity of invention was found during the International Preliminary Examination, noting the first page of the IPER (Form PCT/IPEA/409-Cover Sheet), with special reference to part III, paragraph IV, which has not been checked by the authorized officer. Indeed, the authorized officer considered all the claims (and also, incidentally, found original claims 1-8 and 10 to meet the novelty, inventive step and industrial applicability requirements).

There is no lack of unity-of-invention, and the PTO is obligated to examine all of applicant's claims. Such is respectfully requested.

Applicant respectfully awaits the results of an examination on the merits.

Respectfully submitted,

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Version with Markings to Show Changes Made

13. (Amended) The method of claim ~~10~~11, wherein said diagnosis of a cardiovascular disease comprises a diagnosis of early atherosclerosis, hypertension or thrombosis.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: FROSTEGARD=1A

In re Application of:	)	Art Unit: 1641
Johan FROSTEGARD	)	Examiner: L. Cook
Appln. No.: 09/720,967	)	Washington, D.C.
Date Filed: April 6, 2001	)	Confirmation No. 8281
For: METHOD OF DIAGNOSING CARDIOVASCULAR DISEASE...	)	~~March 29, 2006~~ Jan. 29, 2003

REPLY TO SECOND RESTRICTION REQUIREMENT

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant is in receipt of Paper No. 10, a second Restriction Requirement mailed January 2, 2003.

Applicant again requests the PTO to acknowledge receipt of applicant's paper filed under §119.

The earlier restriction requirement has been substantially repeated, except now the examiner has established a third group, i.e. Group III, thereby compounding the erroneous action made in the first restriction requirement. Nevertheless, as applicant is compelled by the rules to make an election, regardless of the propriety of the requirement, applicant hereby again provisionally and

Attachment B

respectfully elects what is identified as Invention A, Group I, presently said by the PTO to comprise claims 11-13, 20-26 and 28-30, again **with traverse** and without prejudice.

Applicant respectfully repeats the Remarks of the Reply filed July 26, 2002, to the first restriction requirement. Applicant respectfully repeats that there is a single general inventive concept as recited in claim 11 which extends through all three groups. Failure of the PTO to live up to the Treaty obligations of the USA under PCT goes beyond unfair. There is no question that the requirement is improper and should be withdrawn, and there is no justification for maintaining the improper requirement.

Applicant again respectfully awaits the results of an examination on the merits.

Respectfully submitted,

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